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REVIEW

Sole and combined vitamin C supplementation can prevent postoperative atrial fibrillation after cardiac surgery: A systematic review and meta-analysis of randomized controlled trials

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We undertook a systematic review and meta-analysis to evaluate the effect of vitamin C supplementation (vitamin C solely or as adjunct to other therapy) on prevention of postoperative atrial fibrillation (POAF) in patients after cardiac surgery. PubMed, Embase, Web of Science, and Cochrane Library were systematically searched to identify randomized controlled trials assessing the effect of vitamin C supplementation in adult patients undergoing cardiac surgery, and the meta-analysis was performed with a random-effects model. Thirteen trials involving 1956 patients were included. Pooling estimate showed a significantly reduced incidence of POAF (relative risk [RR]: 0.68, 95% confidence interval [CI]: 0.54 to 0.87, $P = 0.002$) both in vitamin C alone (RR: 0.75, 95% CI: 0.63 to 0.90, $P = 0.002$) and as an adjunct to other therapy (RR: 0.32, 95% CI: 0.20 to 0.53, $P < 0.001$). The results remain stable and robust in subgroup and sensitivity analyses, and trial sequential analysis also confirmed that the evidence was sufficient and conclusive. Additionally, vitamin C could significantly decrease intensive care unit length of stay (weighted mean difference: −0.24 days, 95% CI: −0.45 to −0.03, $P = 0.023$), hospital length of stay (weighted mean difference: −0.95 days, 95% CI: −1.64 to −0.26, $P = 0.007$), and risk of adverse events (RR: 0.45, 95% CI: 0.21 to 0.96, $P = 0.039$). Use of vitamin C alone and as adjunct to other therapy can prevent POAF in patients undergoing cardiac surgery and should be recommended for patients receiving cardiac surgery for prevention of POAF.

KEYWORDS
Cardiac Surgery, Postoperative Atrial Fibrillation, Vitamin C

1 | INTRODUCTION

Despite advances in surgical technique, anesthesia, and postoperative care, the incidence of postoperative atrial fibrillation (POAF) remains unchanged. It is reported that the incidence of atrial fibrillation (AF) after cardiac surgery is 17% to 33%.[1–3] Though it is self-limited and 80% of patients return to sinus rhythm after treatment, POAF is significantly associated with increased risk of neurocognitive disorders[4] and septicemia,[5] and consequently results in prolonged hospital or intensive care unit (ICU) stay.[6]

Although the pathophysiology remains unclear, increasing evidence suggests that oxidative stress plays an important role in the pathophysiology of POAF.[7] Numerous pharmacologic interventions attempt to reduce the incidence of POAF; all of them have limitations and adverse effects.[8] It is reported that vitamin C is a promising and cost-effective prophylactic therapy for POAF, and several meta-analyses of randomized controlled trials (RCTs) of vitamin C for arrhythmia prophylaxis have been published.[9–12] Though they all demonstrated that vitamin C could reduce the incidence of POAF, the

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study design and quality of included studies are poor. Considering these limitations and continuing controversy, we therefore undertook a systematic review and meta-analysis to evaluate vitamin C and its adjunctive effect with other therapy in the prevention of POAF in patients undergoing cardiac surgery.

2 | METHODS

We performed this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13] Because all analyses are based on previous published studies, ethical approval and patient consent are waived.

2.1 | Literature search and selection criteria

PubMed, Embase, Web of Science, and Cochrane Library from their inception to March 10, 2018, were searched to identify relevant RCTs assessing the effect of vitamin C supplementation on prevention of POAF after cardiac surgery. Free texts and subject terms were combined (the detailed search strategy is shown in the Supporting Information, Appendix, in the online version of this article). Reference lists of identified studies were manually checked, and the process was performed iteratively until no additional articles could be identified.

The following inclusive selection criteria were applied: (1) study design: RCT; (2) study population: adult patients undergoing cardiac surgery; (3) intervention: vitamin C supplementation (vitamin C solely or as adjunct to other therapy); (4) comparison: placebo or control (other therapy); and (5) outcome measure: the incidence of POAF.

2.2 | Data extraction and outcome measure

Two investigators independently extracted the following data on the studies using a standardized and piloted data spreadsheet: first author, year of publication, sample size, patient characteristics (age and percentage of male patients), surgery type, study design, vitamin C group, control group, definition of POAF, incidence of POAF, hospital length of stay (HLOS), ICU length of stay, and adverse events in each group. The extracted data were checked by another investigator. Any discrepancies were resolved by consensus and discussion. The primary outcome was the incidence of POAF; secondary outcomes included ICU length of stay, HLOS, and adverse events.

2.3 | Risk of bias and GRADE assessment

The qualities of each study's contributing evidence were evaluated following the recommended Cochrane risk-of-bias tool respecting 7 domains—selection (random and allocation), performance, detection, attrition, reporting, and other bias—and each study was assessed to have either low, unclear, or high risk of bias.

Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) are applied for evaluating the level of evidence and strength of recommendations as follows: high quality: further research is very unlikely to change our confidence in the estimate of effect; moderate quality: further research is likely to have influence on our confidence in the estimate of effect and may change the estimate; low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality: we are very uncertain about the estimate.

2.4 | Trial sequential analysis

To avoid increased risk of producing type I error in the meta-analysis by sparse data and repetitive testing of accumulating data, trial sequential analysis (TSA) is applied to determine whether the evidence is reliable and conclusive. When the cumulative z curve crosses the trial sequential monitoring boundary or the futility area, the level of evidence for the intervention is sufficient and no further trials are needed. If the z curve does not cross any of the boundaries, then there is insufficient evidence to reach a conclusion and further studies are still necessary. In the current study, we calculated the required information size for TSA using an α error of 0.05, a β error of 0.20, an anticipated relative risk [RR] reduction of 20% in POAF, and a control event proportion calculated from the control group in our meta-analysis.

2.5 | Statistical analysis

Differences were expressed as RR with 95% confidence intervals (CI) for dichotomous outcomes, and weighted mean differences (WMDs) with 95% CIs for continuous outcomes. Heterogeneity across studies was assessed by using the I^2 statistic, which is a quantitative measure of inconsistency due to heterogeneity rather than chance. Studies with an I^2 statistic of 25% to 50% were considered to have low heterogeneity, those with an I^2 statistic of 50% to 75% were considered to have moderate heterogeneity, and those with an I^2 statistic of >75% were considered to have high heterogeneity.[14] All meta-analyses were performed by using random-effects models. Publication bias was assessed by visually inspecting the Begg funnel plots in which the log RRs were plotted against their standard errors. Publication bias was also detected by Begg and Egger tests.[15,16] A 2-tailed $P < 0.05$ was considered significant, except where a certain P value has been given. All statistical analyses were performed using Stata version 12.0 software (StataCorp LP, College Station, TX); TSA software version 0.95 beta (Copenhagen Trial Unit, Copenhagen, Denmark; http://www.ctu.dk/tsa) was used for TSA analysis.

3 | RESULTS

3.1 | Study identification and selection

The initial database search yielded a total of 396 relevant publications, and 23 records were retrieved through manual search. Eighty-six were excluded because they were duplicated studies, and 333 studies were excluded based on titles and abstracts. The full text of the remaining 26 trials was reviewed for detailed evaluation, and 17 RCTs were included in qualitative synthesis. Finally, 13 trials were involved for quantitative analysis.[17–29] The flow chart of study selection is shown in Figure 1.

TABLE 1 Main characteristics of RCTs included in the meta-analysis

Study ID	Area	No. of Patients (Vitamin/Control)	Age, y[a]/ Male Sex	Surgery Type	Vitamin Group	Control Group	Outcome Measures	Definition of POAF
Vitamin C vs control								
Antonic et al, 2017	Slovenia	105 (52/53)	65.02 ± 9.12/ 78.1%	CABG	Vitamin C: 2 g, IV, at 24 h and 2 h before surgery; 1 g, IV, b.i.d., postop 1st day to postop 5th day	Control (no vitamin C)	POAF, ICULOS, HLOS, AEs	An episode of AF or flutter lasting >10 min or the requirement for an urgent intervention
Bjordahl et al., 2012	USA	185 (89/96)	≥18/67%	CABG	Vitamin C: 2 g, p.o., the night before surgery; 1 g, p.o., b.i.d., postop 1st day to postop 5th day	Control (placebo)	POAF, ICULOS, HLOS, AEs	An episode of AF lasting >10 min or the requirement for urgent intervention
Colby et al, 2011	USA	24 (13/11)	≥18/79%	Cardiac surgery	Vitamin C: 2 g, p.o., the night before surgery; 500 mg, p.o., b.i.d., the day of surgery to postop 4th day	Control (placebo)	POAF, ICULOS, HLOS	Any documented AF lasting >5 min occurring between the day of surgery and postop 4th day
Donovan et al, 2012	USA	294 (150/144)	≥18/NR	Cardiac surgery	Vitamin C: 2 g, p.o., the night before surgery; 1 g, p.o., b.i.d., the day of surgery to postop 5th day	Control (no vitamin C)	POAF	NR
Papoulidis et al, 2011	Greece	170 (85/85)	≥65/71%	CABG	Vitamin C: 2 g, IV, 3 h before CPB; 0.5 g, IV, b.i.d., postop 1st day to postop 5th day	Control (placebo)	POAF, HLOS, AEs	An episode of AF lasting >10 min or the requirement for urgent intervention
Polymeropoulos et al., 2015	Greece	22 (11/11)	>18/59.1%	Cardiac surgery	Vitamin C: 2 g, IV, 2 d before surgery; postop 1st day to postop 4th day	Control (placebo)	POAF, AEs	NR
Sadeghpour et al, 2015	Iran	290 (113/177)	≥18/65.9%	Cardiac surgery	Vitamin C: 2 g, IV, operation day; 1 g, p.o., q.d., postop 1st day to postop 4th day	Control (placebo)	POAF, ICULOS, HLOS, AEs	NR
Sarzaeem et al, 2014[32]	Iran	170 (85/85)	59.10 ± 9.80/ 69.4%	CABG	Vitamin C: 2 g, IV, 12 h before surgery; 0.5 g, IV, b.i.d., postop 1st day to postop 5th day	Control (placebo)	POAF, ICULOS, HLOS	An episode of AF lasting ≥10 min or requiring immediate therapeutic intervention
Van Wagoner et al, 2003	USA	346 (177/169)	64.1/NR	CABG	Vitamin C: 2 g, p.o., the night before surgery; 500 mg, p.o., b.i.d., the day of surgery to postop 5th day	Control (placebo)	POAF, HLOS, AEs	NR
Vitamin C + other vs control + others								
Dehghani et al, 2013	Iran	100 (50/50)	>50/74%	CABG	Vitamin C: 2 g, p.o., before surgery; 0.5 g, p.o., b.i.d., postop 1st day to postop 5th day; β-blocker: 1 weeks before surgery and continued after surgery	Control (no vitamin C); β-blockers: 1 wk before and continued after surgery	POAF, ICULOS, HLOS, AEs	An episode of AF lasting >10 min
Eslami et al, 2007	Iran	100 (50/50)	>50/67%	CABG	Vitamin C: 2 g, p.o., the night before surgery; 1 g, p.o., b.i.d., postop 1st day to postop 5th day; β-blockers: before surgery and continued after surgery	Control (no vitamin C); β-blockers: before surgery and continued after surgery	POAF, ICULOS, HLOS, AEs	An episode of AF lasting >10 min or the requirement for urgent intervention
Healy et al, 2010	USA	30 (19/11)	≥18/NR	CABG	Vitamin C: NR; β-blockers: NR	Control (NR); β-blockers: NR	POAF	NR
Samadikhah et al, 2015	Iran	120 (60/60)	60.50 ± 11.30/ 68.3%	CABG	Vitamin C: 2 g, p.o., on surgery day and 1 g, p.o., q.d., postop 2nd day to postop 5th day; Atorvastatin: 40 mg, p.o., on surgery day to postop 5th day	Control (placebo); atorvastatin: 40 mg, p.o., operation day to postop 5th day	POAF	NR

Abbreviations: AE, adverse event; AF, atrial fibrillation; b.i.d., twice daily; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; HLOS, hospital length of stay; ICULOS, intensive care unit length of stay; IV, intravenous; NR, not reported; p.o., oral administration; POAF, postoperative atrial fibrillation; postop, postoperative; q.d., once daily; RCT, randomized controlled trial; SD, standard deviation.

[a] In some studies age is presented as mean ± SD.

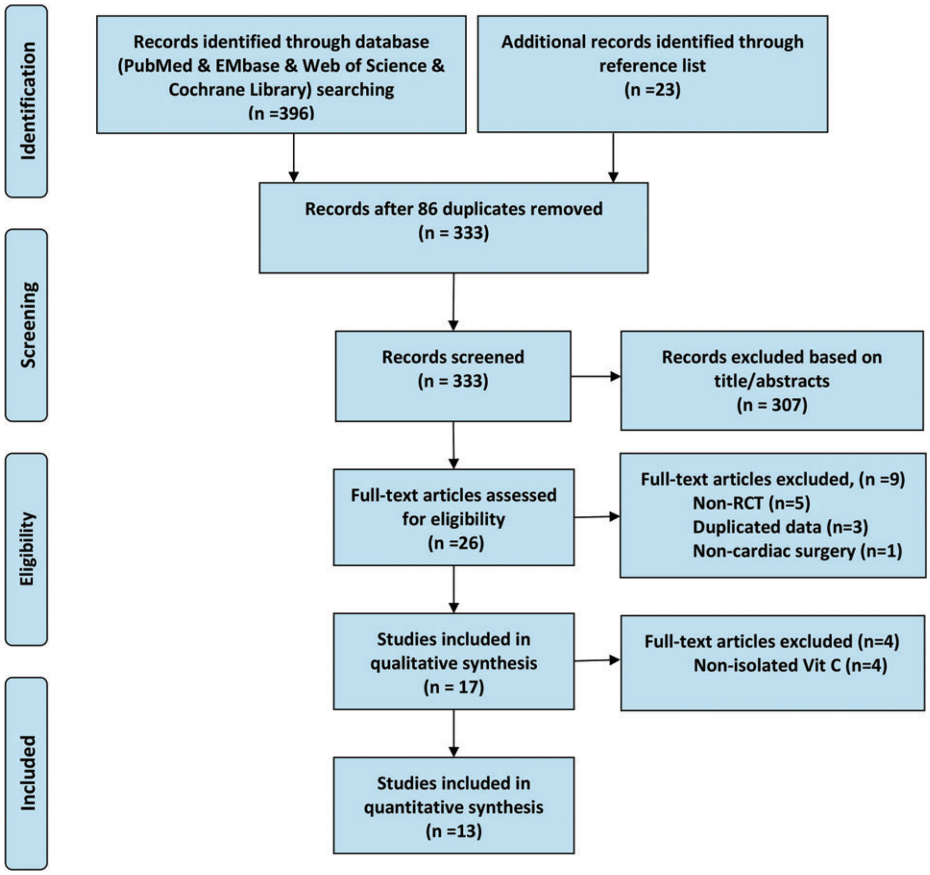

FIGURE 1 Flow chart of the selection process for studies included in the systematic review and meta-analysis. Abbreviations: RCT, randomized controlled trial; vit C, vitamin C

3.2 | Characteristics of eligible studies

The main characteristics of the thirteen RCTs included in the meta-analysis and systematic review are shown in the Table 1 and separately in the Supporting Information, Table S1, in the online version of this article. The outcome data of each included trial are presented in the Supporting Information, Table S2, in the online version of this article. The studies were published between 2003 and 2017, and sample sizes ranged from 22 to 346 patients, with a total of 1956. Patients in nine trials underwent coronary artery bypass grafting (CABG), and patients underwent CABG and/or valve surgery in the remaining four trials. Though the definition of POAF varied among the trials, the main characteristic is an episode of AF lasting beyond a certain period or requiring urgent intervention. Among the thirteen included studies, all reported the POAF events; eleven of them reported it as the primary outcome[17,18,20–24,26–29]; nine of them reported HLOS[17–22,24,25,27]; eight reported ICU length of stay[17–20,22,24,25,27]; and eight reported the adverse events.[17–22,24,25] The risk of bias of the included studies was high in three studies, unclear in five studies, and low in five studies (Figure 2).

3.3 | The primary outcome: POAF

Of 1956 patients involved in all thirteen included studies contributing POAF data, 48.8% of patients received vitamin C supplementation and 51.2% of controls developed POAF. The pooled RR using a random-effects model showed that vitamin C supplementation significantly reduced the incidence of POAF (RR: 0.68, 95% CI: 0.54 to 0.87, P = 0.002; Figure 3), with moderate heterogeneity among the studies (P for heterogeneity = 0.003; I^2 = 59.2%). Further exclusion of any single study did not materially alter the overall combined RR, with a range from 0.64 (95% CI: 0.49 to 0.84) to 0.72 (95% CI: 0.57 to 0.91). As shown in Figure 4, trial sequential analysis showed that the z curve entered the area of benefit with crossing the conventional boundary for benefit and trial sequential monitoring boundary for benefit, indicating that the evidence was sufficient and conclusive and further studies are not needed.

3.4 | Subgroup and sensitivity analyses

The results of subgroup and sensitivity analyses are shown in the Supporting Information, Figure S1, in the online version of this article. Vitamin C supplementation solely was associated with a significantly reduced incidence of POAF (RR: 0.75, 95% CI: 0.63 to 0.90, P = 0.002), and a significant decreased incidence of POAF was observed when vitamin C was used as an adjunct to β-blocker (RR: 0.29, 95% CI: 0.16 to 0.53, P < 0.001) and statin (RR: 0.40, 95% CI: 0.17 to 0.96, P = 0.040). The overall effect of vitamin C as adjunct to routine treatments (β-blocker, statin) on prevention of POAF is much more significant than vitamin therapy alone, as there was no overlap between the 95% CIs (RR: 0.32, 95% CI: 0.20 to 0.53, P < 0.001 vs RR: 0.75, 95% CI: 0.63 to 0.90, P = 0.002). As for surgery type, vitamin C supplementation was associated with a significantly reduced incidence of POAF in CABG (RR: 0.60, 95% CI: 0.43 to 0.83,

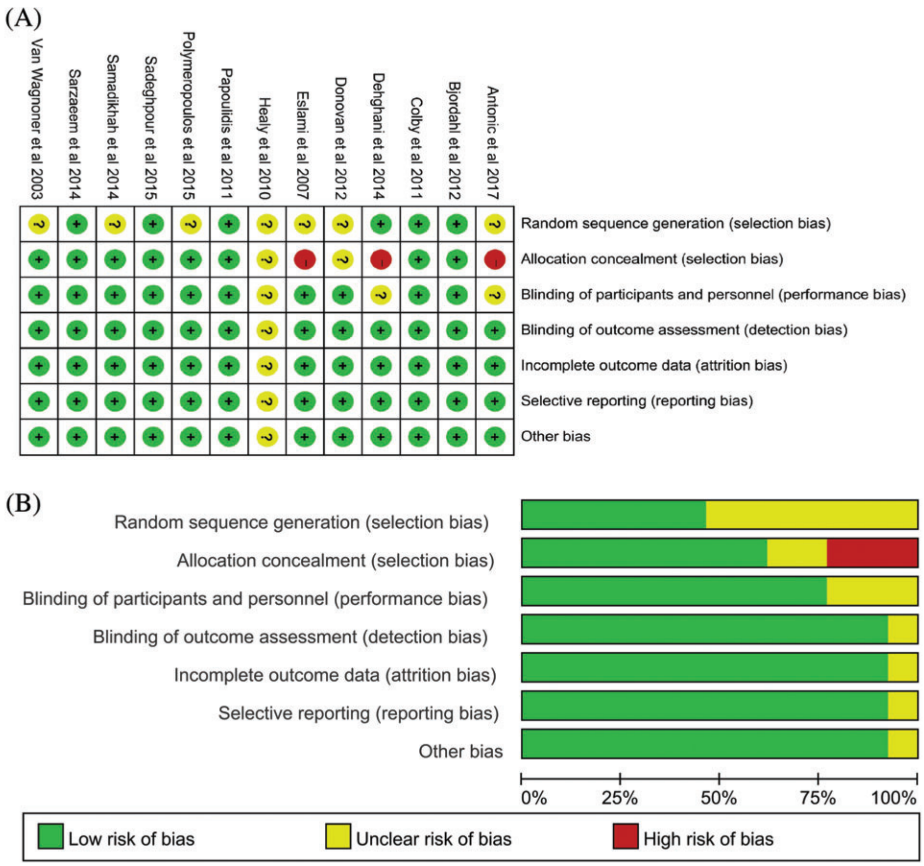

FIGURE 2 Quality assessments concerning risk of bias. (A) Risk-of-bias summary: judgments about each risk-of-bias domain for each included study. (B) Risk-of-bias graph: judgments about each risk-of-bias domain presented as percentages across all included studies

P = 0.002), but not in valve surgery/CABG (RR: 0.82, 95% CI: 0.54 to 1.25, *P* = 0.359). Additionally, the results of subgroup analyses according to most other factors were consistent with a pooled estimate.

3.5 | Secondary outcomes

Vitamin C supplementation also was associated with a shorter ICU length of stay (WMD: −0.24 days, 95% CI: −0.45 to −0.03, *P* = 0.023) and HLOS

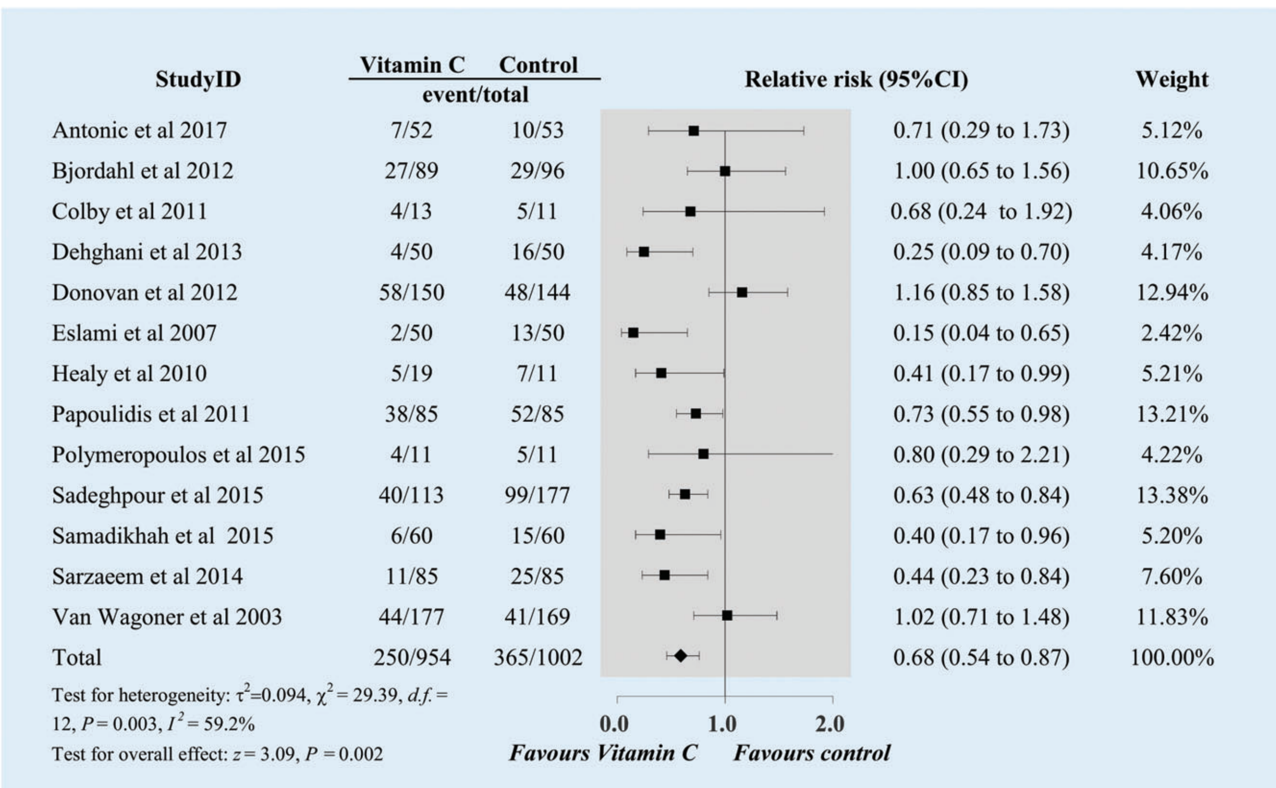

FIGURE 3 Pooled estimates of RCTs evaluating effects of vitamin C on the incidence of POAF with random-effects model. Abbreviations: CI, confidence interval; d.f., degrees of freedom; POAF, postoperative atrial fibrillation; RCT, randomized controlled trial

(WMD: −0.95 days, 95% CI: −1.64 to −0.26, *P* = 0.007; see Supporting Information, Figures S2 and S3, respectively, in the online version of this article). A significant difference in adverse events was observed between the 2 groups (RR: 0.45, 95% CI: 0.21 to 0.96, *P* = 0.039; see Supporting Information, Figure S4, in the online version of this article).

3.6 | GRADE assessment and publication bias

Results of GRADE assessment are described the Supporting Information, Table S3, in the online version of this article. The grading levels of evidence according to the GRADE Working Group were high for the POAF and adverse events and moderate for ICU length of stay and HLOS. Possible publication bias was detected by visually inspecting funnel plot, the Egger test with a *P* value of 0.042, and the Begg test with *P* value of 0.200, indicating a moderate likelihood of publication bias (the Supporting Information, Figure S5, in the online version of this article). However, the power of the test was low because of the limited number of studies included.

4 | DISCUSSION

This further systematic review and meta-analysis of RCTs evaluating the efficacy of vitamin C on prevention of POAF in patients undergoing cardiac surgery suggested that vitamin C itself and combined vitamin C could prevent POAF, and that vitamin C as an adjunct to routine therapy (eg, statin, β-blocker) exerts a stronger preventive effect than vitamin C alone. Additionally, vitamin C supplementation was associated with a markedly shorter ICU length of stay and HLOS and reduced risk of adverse events.

The mechanism of POAF benefit from vitamin C supplementation has not been fully clarified. However, growing evidence supports that oxidative stress and inflammation triggered by the cardiac surgery play a vital role in the pathogenesis of POAF.[30] Based on the pathogenic role of oxidative stress and inflammation, vitamin C, as an antioxidant, may reduce POAF by scavenging superoxide anion and attenuating inflammation.[31] Additionally, it was reported that vitamin C could down-regulate the major enzyme for oxidative stress, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and tetrahydrobiopterin, and thus attenuate the production of superoxide.[32] On the contrary, due to the abrogation of superoxide production, the beneficial effects from the ischemia preconditioning could also be abolished by vitamin C.[33] As an adjunct to other therapy (β-blockers or statins) for the prevention of POAF, evidence suggested that vitamin C combined with a β-blocker was more effective than a β-blocker alone. Therefore, a synergistic effect among vitamin C and β-blockers or statins might exist,[22] but there is still need for further clarification to confirm the synergistic effect. On the other hand, it is noteworthy that investigations about the preventive effect of vitamin C on POAF should not only merely focus on the antioxidant power, but also should pay attention to the potential biologic properties, for it might overwhelm the antioxidant effects of vitamin C.

Four studies included in our systematic review compared the prevention effect on POAF between vitamin C, as an adjunct to ω-3 polyunsaturated fatty acid (PUFA) and vitamin E, and placebo.[34–37] All demonstrated that antioxidant supplementation could significantly decrease the risk of POAF after cardiac surgery, indicating a potential preventive effect of vitamin C on POAF. However, this benefit also might be owing to ω-3 PUFA and vitamin E. In the current study, we demonstrated that supplementation with vitamin C alone could prevent

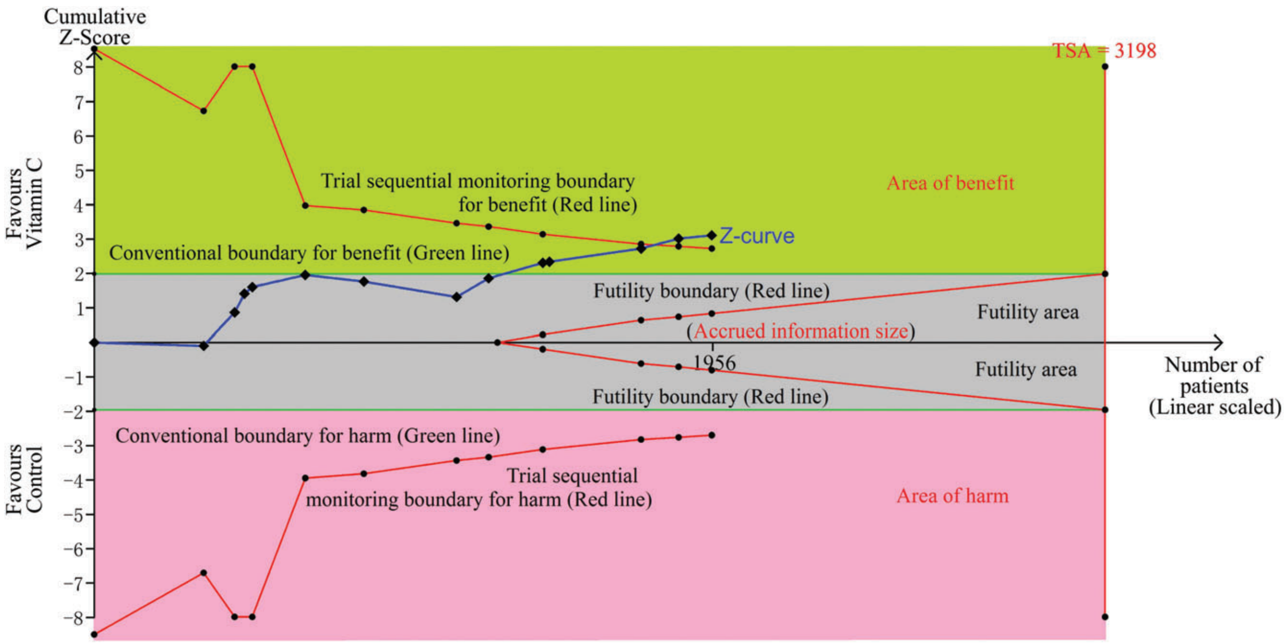

FIGURE 4 Trial sequential analysis of 13 RCTs (black square fill icons) illustrating that the cumulative *z*-curve crossed both the conventional boundary for benefit and the trial sequential monitoring boundary for benefit and entered the area of benefit, establishing sufficient and conclusive evidence, suggesting further trials are not needed. A diversity adjusted required information size of 3198 patients was calculated using an α error of 0.05, a β error of 0.20 (power 80%), an anticipated RR reduction of 20% in POAF, and a control event proportion of 36.4, calculated from the control group in our meta-analysis. Abbreviations: POAF, postoperative atrial fibrillation; RCT, randomized controlled trial; RR, relative risk

POAF after cardiac surgery. Additionally, the beneficial effect also existed in vitamin C as an adjunct to a statin or β-blocker, and a stronger additional preventive effect than vitamin C alone was observed.

Several meta-analyses[9–12] on this issue also confirmed the preventive role of vitamin C on POAF (see Supporting Information, Table S4, in the online version of this article). However, subgroup or sensitivity analyses were not performed in most of them, and cohort studies were included in the study by Polymeropoulos et al.[12] Non-RCTs were treated as RCTs and involved for meta-analysis in 3 meta-analyses,[9–11] and study of noncardiac surgery was analyzed in the study by Hemilä et al.[10]

Though consistent with previous meta-analyses, the main finding of this updated meta-analysis generally concurs with and further extends the finding of the previous ones in several important ways. Our meta-analysis reinforces earlier results by including the studies recently published and conducting sufficient subgroup and sensitivity analysis based on predesigned potential factors about clinical and study method. Additionally, TSA for power analysis was applied, and sufficient and conclusive evidence was verified in our research. Furthermore, application of vitamin C in patients undergoing cardiac surgery was evaluated by GRADE assessment, and the quality of evidence was high on prevention of POAF, whereas this assessment was absent in previous meta-analyses. Moreover, the current study also evaluates the effect of vitamin C as an adjunct to other therapies in the prevention of POAF, and a synergistic effect among vitamin C and β-blockers or statins might exist and result in a strengthened preventive effect on POAF.[20,22,23,26]

Results of subgroup and sensitivity analyses were inconsistent with the overall pooled estimate when grouped by geographical area, sample size, control, and surgery type. Inconsistency between controls and sample size could be explained by the placebo effect, methodology of allocation concealment, and statistical test power. In our study, relatively lower heterogeneity (I^2 = 22.4%) in the subgroup of the Eastern area and relatively higher heterogeneity (I^2 = 47.5%) in the subgroup of the Western area were observed. Because the included studies were all RCTs, the clinical heterogeneity is the main source of statistical heterogeneity. Though no significant benefit was observed in the Western area, a beneficial trend of decreased RR was observed. Therefore, the difference between Western and Eastern areas might be attributed to clinical heterogeneity. Inconsistent results of surgery type on the effect of vitamin C should be explained as follows: coronary heart diseases are associated with inflammatory responses and lipid deposition, whereas valvular diseases are mostly related to the aging process due to calcification of valves. Therefore, patients with valve surgery had a relatively lower risk of POAF and failed to benefit from vitamin C's scavenging the superoxide anion and attenuating inflammation. Because subgroup and sensitivity analyses are observational by nature, misleading results could be drawn, and thus these findings should be treated with caution.

Both previous meta-analyses and the current study showed that vitamin C supplementation was associated with a shorter HLOS and ICU length of stay, which provides more compelling evidence of tangible benefit for clinicians than simply reducing the incidence of POAF. This is of great importance, as shorter lengths of stay may reduce the risk of nosocomial infection and thus result in a financial benefit.

According to our findings, vitamin C should be recommended as an effective and economical measure for patients receiving cardiac surgery for prevention of POAF, especially for patients undergoing CABG. It could be given alone or as an adjunct to other strategies (eg, statin, β-blocker), and the latter approach was encouraged. However, what should additionally be noted is that vitamin C has been reported to be associated with several adverse events, especially at relatively high doses, though no significant adverse events were observed in our analysis. In one study, patients with sickle-cell anemia received antioxidant vitamins C and E; these were not beneficial for anemia and led to increased hemolytic markers.[38] Additionally, accumulating evidence that vitamin C may cause kidney stones has been confirmed by large studies, which found that vitamin C intake in excess of 1000 mg/d was associated with increased risk of symptomatic kidney stones in men,[39] but not in women.[40] Thus, high-dose intake of vitamin C should be avoided.

4.1 | Study limitations

Some limitations of this study should be taken into account. First, there is a moderate heterogeneity among the included RCTs, which can be attributed to differences in patient characteristics, study design, and definitions of POAF. Nevertheless, the results remain consistent and robust in our subgroup and sensitivity analyses. Second, among the 13 included RCTs, 2 reported POAF consistently, rather than a primary outcome[19,34]; and 1 only enrolled 22 patients, with a modest sample size.[19] This leads to potential underestimation and/or overestimation of the true incidence of POAF because of the low test power. Third, none of the included RCTs provided a cost-effectiveness analysis; thus, this could not be explored and it may be an interesting focus for future studies. Finally, several included studies were performed in a single geographic region (Iran), which played a predominant role in the pooled estimate and might cause potential bias.

5 | CONCLUSION

In summary, the prophylactic use of vitamin C alone and as an adjunct to other therapy can prevent POAF in patients undergoing cardiac surgery. Therefore, vitamin C should be recommended for prevention of POAF in patients undergoing cardiac surgery, and its use as an adjunct to other strategies was encouraged.

Conflicts of interest

The authors declare no potential conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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